

## **Title**

User experiences of development of dependence on the synthetic cannabinoids, 5f-AKB48 and 5F-PB-22, and subsequent withdrawal syndromes.

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**Conflict of Interest:** Authors declare no conflict of interest.

## Abstract

### *Rationale*

Emergence of synthetic cannabinoids (SCBs) in herbal smoking mixtures is a public health concern. New SCB's such as 5f-AKB48 and 5F-PB-22 have been detected in French seizures and in sudden death post mortems in the US.

### *Objectives*

The aim was to describe development of dependence on herbal smoking mixtures containing the SCB's, 5f-AKB48 and 5F-PB-22 and subsequent withdrawal syndromes.

### *Methods*

Dependent users of herbal smoking mixtures known to contain the SCB's 5f-AKB48 and 5F-PB-22 with an average Severity of Dependence Score (SDS) of 13 were interviewed using a structured guide (three males/three females). Narratives were analysed using the Empirical Phenomenological Psychological (EPP) five step method. Six themes with 68 categories emerged from the analysis.

### *Results*

Themes are illustrated as 1) Networks and Product Availability; 2) Drivers and Motives for Use; 3) Effect and Pathways toward Dependence; 4) Poly Substance Use and Comparisons to Natural Cannabis; 5) Dependence and Withdrawal and 6) Self-detoxification Attempts. Two higher levels of abstraction above these theme-levels emerged from the data, with sole use of herbal smoking mixtures containing 5f-AKB48 and 5F-PB-22 centering on the interplay between intense cravings, compulsive all-consuming seeking, use and re-dose behaviours, and fear of the psychiatric and self-harms caused when in withdrawal.

### *Conclusions*

This is the first study describing dependence and withdrawal experiences in users dependent on 5f-AKB48 and 5F-PB-22. Given the potential for adverse psychiatric and physical consequences of dependent use, further development of specific clinical responses and clinical research around toxicity and withdrawal severity are warranted.

## Key Words

Synthetic cannabinoid; 5f-AKB48; 5F-PB-22; Herbal cannabis, Spice, withdrawal

## Introduction

The phenomenon of commercially available psychoactive products containing one or more synthetic cannabinoids (SCBs) in herbal smoking mixtures remains a serious public health concern (Bretns and Prather 2014; Gunderson et al. 2012; Seely et al. 2012; Spaderna et al. 2013). Known as ‘*K2*, *Spice and Kronic*’ (Bright et al. 2013; Baumann et al. 2014; Fantegrossi et al. 2014), an ever diverse range of SCBs are manufactured and designed for circumvention of contemporary legislative controls (Vandrey et al. 2012). The occurrence of SCBs was recognised in Europe as early as 2004 when sold as ‘*legal highs*’ or ‘*herbal highs*’ (Bryner 2010; Deluca et al. 2009; Griffiths et al. 2010; Schifano et al. 2009; Seely et al. 2011). Diverse forms of manufacture are evident with SCBs sprayed onto plant material (generally about 3g), and subsequently dried, crushed and packaged as powdered, loose leaf or pre rolled mixtures (Zuba et al. 2011; Kikura-Hanajiri, et al. 2011). Many European nations (Austria, Germany, France, Luxembourg, Poland, Lithuania, Sweden and Estonia) took legal actions to ban or control SCBs by 2009 (EMCDDA 2009), with other nations (United States (US), Australia, New Zealand) following suit (Dargan et al. 2011). Trends in use have displaced outside of Europe, and to countries including the United States (US), Australia, New Zealand, Japan, and Taiwan (Fattore and Fratta 2011; Grigoryev et al. 2011a,b; Seely et al. 2011). Despite efforts to regulate and reduce harm, use of herbal smoking mixtures containing SCBs have been reported as popular among Australian young adults, and particularly those who have previously used cannabis (Barratt et al. 2013). US longitudinal data in 2015 however indicates a downward trend in popularity among both school aged children since 2013 (Johnston et al. 2015) and in college students (Egan et al. 2015).

SCBs in contrast to phytocannabinoids (delta-9-tetrahydrocannabinol or THC) are high potency, high efficacy cannabinoid receptor full agonists (Lindigkeit et al. 2009; Tuv et al. 2012; Vardakou et al. 2010). Commonly identified SCBs such as JWH-018, JWH-073 and CP-47,497 bind and activate the cannabinoid receptors CB1R and CB2R with exceptional potency and efficacy

(Bretons and Prather 2014; Gunderson et al. 2012; Seely et al. 2011). Generally they exhibit similar effects to high dose cannabis, but are potentially more harmful (Hermanns-Clausen et al. 2013). SCBs are constantly innovating, with new generation designer cannabinoids emerging such as the aminoalkylindole JWH-073 (Auwärter et al. 2009; Lindigkeit et al. 2009), the hexyl homolog JWH-019 (Dresen et al. 2011), and the more recent aminoalkylindoles, JWH-250 (Westphal et al. 2010) and JWH-398 (Hudson et al. 2010). Other market entries since 2010 include JWH-015, JWH-122, HU-210 and AM-694 (EMCDDA 2009; Ernst et al. 2011). More recently, 5F-AKB-48 was detected in French seizures (Roussel et al. 2015) and 5F-PB-22 in sudden deaths post mortems in the US (Behonick et al. 2014).

Concerns around use of SCBs are compounded by the fact that these ever diverse range of new designer cannabinoids have the potential to cause significant adverse events following use and have not been rigorously tested in human clinical trials (Auwarter et al. 2009; Hillebrand et al. 2010; Seely et al. 2012). Clinical case presentation and user reporting of negative medical, psychiatric and social consequences is evident (Spaderna et al. 2013). Chronic use of SCBs can result in serious cognitive impairment and development of dependence (Fattore and Fratta 2011; Vardakou et al. 2010; Zimmermann et al. 2009). The aim of this study was to describe user's experiences of development of dependence on 5f-AKB48 and 5F-PB-22, and their subsequent experiences of attempting to withdraw. There is little published data regarding this phenomenon, despite withdrawal units and hospitals around the world providing case examples of the wide range of withdrawal syndromes ranging from very mild to that of psychotic symptoms and seizures, despite the reporting of smoking of similar amounts of herbal smoking mixtures (Zimmerman et al. 2009; Vearrier and Osterhoudt 2010; Müller, et al. 2010a; Hurst et al. 2011; Castellanos et al. 2011; Schneir et al. 2011; Van der Veer and Fiday 2011; Simmons et al. 2011; Tung et al. 2012; Gunderson et al. 2012; Bebarta et al. 2012; Berry-Caban et al. 2013; Rominger et al. 2013).

## Methods

The study was undertaken in 2015 in the north-east of the Republic of Ireland, as part of a larger research project investigating the availability and use of herbal smoking mixtures. At the time, community care and mental health services reported concern for cross border drug tourism of novel psychoactive substances (NPS), littering of herbal product paraphernalia, increased crisis presentations at emergency health services and youth deaths by suicide speculated to be linked to psychotic symptoms when in withdrawal.

A structured interview guide was developed by the research team on basis of extant available literature on SCBs, and active consultation with key professionals operating (n=3) in the area. Participants identified as using the available herbal mixtures containing 5f-AKB48 and 5F-PB-22 were recruited with assistance from a local community outreach worker who acted as gatekeeper. Dependent users were screened for inclusion based on the Severity of Dependence Screener (SDS) (Gossop et al. 1995) which is a 5-item questionnaire, with scores of over 7 deemed to indicate dependence in the past 12 months. This screening tool has been used in a previous SCB study to distinguish between casual and dependent users (Gunderson et al. 2014). Three male (aged 17-38 years) and three female (20-42 years) dependent users of mixtures containing 5f-AKB48 and 5F-PB-22 were interviewed. The average SDS score was 13, and with two scoring the maximum score of 15 (one male, one female), two scoring 13 (two males), two female scores of 9 and 13 respectively.

The study was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki, and the institute's ethical policies for conducting research. All participants received an information sheet and gave written informed consent prior to the interview. All were assured of confidentiality and anonymity, and that they could withdraw from the study if requested. In depth interviews of 30-90 minutes were conducted in a private room at the community service setting, and captured illustrative data pertaining to the user's experiences of dependence and withdrawal phenomena. Audio recordings were destroyed post transcription.

The data-set was analysed using the Empirical Phenomenological Psychological (EPP) five step method (Karlsson 1995). This approach is underpinned by Husserl's (1970) phenomenology theory, and focused on the realist description of the *'life world'* user's experience of dependence trajectories and withdrawal syndromes. See Table 1.

*Insert Table 1 about here*

Six themes emerged from the analysis. During the final step in the analysis process, two additional higher levels of abstraction above the theme-level emerged from the data, firstly with use of herbal smoking mixtures centering on the interplay between intense cravings, compulsive all-consuming drug seeking and using behaviours, and secondly inability to cease use with fear of the psychiatric harms caused when in withdrawal. The raw data were re-read by both members of the research team with these two concepts described by the majority participants in distinct ways.

## **Results**

### *Networks and Product Availability*

A variety of products containing 5f-AKB48 and 5F-PB-22 were in circulation (*'Clockwork Orange'*, *'Happy Joker'*). Online sourcing of information and bulk purchasing via web retailers, sourcing via local market retail, border drug tourism and door to door delivery were described. One participant described the use of car *'blaring loud music like the ice-cream man'* as indicating presence of dealers in the estate. Awareness of potential adverse consequences of use was low and primarily reliant on perception of safety grounded in legal status, informal peer user dissemination, and if accessing community services on the provision of harm reduction leaflets by staff.

*'It shouldn't be legal. It shouldn't be allowed, it is terrible, it's killing us all.'*

Participants described spending between €60 -200 per week for personal use. Some described large debts accruing over short timeframes due to compulsive use.

*'I could use three or four bags a day. They give it out on tick, these dealers like. That could go on until you run up a bill of maybe €300 or €400, it's crazy.'*

Some participants described spending their parent's money as well as their own social benefit. Many described personal neglect due to the cost involved.

*'Maybe near €200 euro. I have often seen myself starving and buying it.'*

Alternative income generation and diversification into dealing was viewed to fuel continued availability, social reinforcement of use and clustering of 'pockets of user networks' within certain estates. Members of these user networks were described as ranging from as young as 13 or 14 years, up to early forties, with increasing patterns of use among females and older individuals.

*'I'd say 70% of XXXX [estate] that, the oldest who smokes it in the park is the lads mother, and the oldest that smokes it is about 42. It doesn't go past 42 years of age.'*

### ***Drivers and Motives for Use***

Widespread availability and affordability (€15-20 per one gram bag) appeared first and foremost as driver for introduction and subsequent use. Boredom and peer socialisation was mentioned by all participants as stimulating initial experimentation.

*'Pure boredom. Sitting at home smoking, sure you're doing nothing anyway, just lying about.'*

Participants reported smoking with no reports of insufflation or injecting. Two reported using a 'bong', with others rolling up with very little tobacco added. Mixed opinions were evident with regard to preferences between rolling up and use of a bong.

*'Through the bong, it's the only way I do it. I smoke it pure and that's the worst way of doing it. You're getting that full hit of everything.'*

In addition to smoking for intoxication purposes (both dissociation and psycho-stimulant), some used to relieve anxiety and boost low mood.

*'I would be a worrier. It would make it better, it freezes it.'*

One participant described use of herbal as quelling voices in their head.

*'There are times when I hear voices in my head telling me to do these things, telling me suicidal thoughts. When I smoke the herbal it seems to kill the voice.'*

### ***Effect and Pathways toward Dependence***

First-time experimentation was described as an intensely pleasurable experience despite nausea. All reported intense desire to repeat the experience again.

*'High as a kite, Felt brilliant, It was just the best feeling I've ever had. You are just feeling so happy, so "up there".'*

Participants described *'warm, happy feelings'*, which occurred within two-10 seconds, receded over seven-20 minutes depending on user tolerance and length of time using the product, and was rapidly replaced by feelings of agitation, restlessness and desire to re-dose during the comedown.

*'Warm feelings, feel brilliant, but then when that feeling goes away, bad. Start feeling angry....'*

Differences in effect were observed, ranging from dissociation to psycho-stimulation, and attributed to the lack of consistency in product quality and content, and the combinations of 5f-AKB48 and 5F-PB-22.

*'You could be chilled out with that one [pointed to packet], you know relaxed. And that one [pointed] your head could be racing.'*

The psycho-stimulant effect of herbal smoking mixtures was characterised by motor restlessness, fear, paranoia and aggression.

*'When you are stoned [on herbal] you're not relaxing, you're jumping you are flinching, like those kinda movements [flinching and jerking movements], it is not good.'*  
(participant)



Experiences of unintentional overdose centred on intense chest pain and severe dissociation.

*'You feel like a heart attack, that you are just gonna die all of a sudden. I'm in a very very deep sleep like.'*

Perceptions of the effect changed over time, from pleasure to user realisation of tolerance, unpleasant withdrawals and fears around stopping use.

*'It is not the same buzz now. It's the addiction, I don't want it for the buzz. Something inside me needs it.'*

Participants described how the duration of effect reduced considerably over time, as tolerance increased. Re-dosing when use was established commonly occurred every 20 minutes within the smoking episode.

*'When I first took it, it'd last an hour. Now 10 or 15 minutes it would be gone... then you do it all over again, all over again, all over again.'*

### ***Poly Substance Use and Comparisons to Natural Cannabis***

All described sole use of these mixtures containing 5f-AKB48 or 5F-PB-22 (or combined) and did not concurrently or sequentially consume any other illicit drugs or alcohol, with exception of when in withdrawals and using natural cannabis/alcohol to alleviate symptoms. All reflected on how they essentially replaced excessive alcohol use and illicit drug use, with the sole and dependent smoking of herbal mixtures.

*'I had a problem with alcohol about five years ago. I went from one addiction and I walked straight into another one. This one is a lot harder to get off than the alcohol.'*

Many had used natural cannabis prior to introduction to mixtures containing 5f-AKB48 and 5F-PB-22. Quality and potency of effect (*'the quick high'*) was a factor in user decision-making, with reports of low availability of poor quality cannabis stimulating displacement to smoking herbal mixtures.

*'It was a quick high, couple drags and you are away.....with herbal you'll get your high any time.'*

### ***Dependence and Withdrawal***

Patterns of established use occurred rapidly, and centred on regular daily smoking. Some only smoked at night (often in response to withdrawals) and were able to attend training activities during the day. Three described using alone, and the remainder in small groups, almost always indoors in private homes.

*'I would do it on my own too, just to get a bit on me own.'*

Participants described using between one and four grams per day, with volume of use increasing quickly following first-time experimentation. Compulsive re-dosing occurred despite recognition of loss of control, awareness of tolerance and fears around adverse effects.

*'I use three gram a day. That'll do me just one day and a 1gram bag is gone in an hours' time. That's how bad it is. I won't stop until it is gone. I know it's killing me. I won't stop it, I just can't'.*

Many described rapid development of thoughts and cravings about smoking first thing in the morning, with one participant walking up in the middle of the night to smoke. This thought-process was observed to occur quite quickly following initial patterns of use of these mixtures.

*'Every 2-3 hours, it is like in a routine, it has your head in a routine. If you told me I'd be dead tomorrow morning from that herbal, I still couldn't give it up. That herbal still has an awful hold on me.'*

Acute physical withdrawal symptoms when attempting to restrict use were reported to include chest pains, chest pressure, tachycardia and palpitations, lower extremity pain and spasms, nausea, sweating and vomiting.

*'Pains and aches come in if you haven't got it. Bad pains across my chest, my heart thumping everyday 100 miles an hour. Flat out thumping non-stop. Then your hands start to sweat.'*

These symptoms were described as easily resolved by resumed smoking of herbal mixtures.

*'If I haven't got it I get the sickness in my stomach, the sweating starts, the weakness starts, the sickness comes then you get the cold shiver through you, but as soon as you get a smoke of the herbal you are back to normal.'*

Psychological withdrawal symptoms including anxiety, agitation and paranoia were illustrated by participants.

*'If you don't have it you feel down, angry. Just bad all the time. Fighting with your family over money that they haven't got. Just do anything to get it.'*

Over time all participants described general decrease in function characterised by loss of appetite, breathlessness, cardiac conditions requiring medication, skin ablations, tooth decay, tremors and insomnia, which were all exacerbated when attempting to reduce use. Difficulties in eating were most common.

*'I'd just look at it [plate of dinner] and take one forkful and say get that away from me, or vomit. It is just that serious. Haven't had a dinner in three or four weeks.'*

Two reported personal awareness and concern for cognitive impairment, characterised by ability to concentrate and short term memory loss. Apathy was a defining characteristic and with associated negative aspects relating to education, training and employment.

*'My attitude is just ridiculous, I'm lazy, don't wanna do nothing.'*

All expressed regret on smoking herbal mixtures given their experience.

*'Herbal is a curse. I wish I could never see it or smoked it or smelled it or anything. It's a curse on everybody in this town to be honest.'*

### *Self-detoxification Attempts*

All described a desire and intentions to stop using, and how the occurrence of unpleasant physical and mental withdrawal symptoms fuelled fears and created barriers to achieving abstinence. Efforts to successfully self-detoxify at home were also hampered by low personal resilience and perceived willpower, and widespread availability in the locality.

*'I would love to stop. I stress out too much. The most I've really stopped it for is a day, or most of a day, or like before going to bed that day I'd have had one.'*

Use of other substances such as alcohol and natural cannabis to assist detoxification attempts was common.

*'I'd use a good bit of it [alcohol] to try not smoke anything.'*

One participant described attempts to return to use of natural cannabis, which was viewed as a lesser of two evils, and more manageable in terms of resuming a normal existence.

*'I am trying to get back on the weed, you can eat properly, you can sleep properly.'*

Two commented that if they were incarcerated, they would be able to cease use. One participant described a self-detoxification attempt when in prison characterised by diarrhoea, insomnia, restlessness, agitation, and sweating, and which was concluded within three weeks but with lasting difficulty with sleeplessness.

*'Diarrhoea, can't sleep, walking the floors, waking every half hour. Wanting a smoke like. It took me a good eight weeks to just get my sleep back to normal like and it took me I'd say a good four weeks for me to be "me".'*

Suicidal ideation and suicide attempts during these times were described by four participants.

*'I don't wanna hurt meself, but it's gonna come that far. I just hate it. So hard to get off it, so hard to do anything. There's only one way of getting off herbal and that's taking yourself out of this life.'*

Experiences of bereavement of peer users who had committed suicide were described by four participants. This contributed to intense fears around coming off herbal mixtures.

*'I lost a brother last year over herbal, lost a best friend over herbal as well. He hung himself. I know it's the herbal that killed them, but I can't stop.'*

Participants expressed desire for residential detoxification and with sufficient length of step down care.

*'To get away from it I need to be put into a clinic. Completely away'.*

## **Discussion**

Studies on NPS in Ireland to date have largely centred on the pre and post legislative sale and supply of headshop products (Kavanagh et al. 2010), and recreational and problematic injecting use of the synthetic cathinone, Mephedrone (McElrath and Van Hout 2011; Van Hout and Bingham 2012; Van Hout and Brennan 2011a,b,c, 2012). This is the first study of its kind focusing on use of SCBs in Ireland. Findings are consistent with other qualitative studies focusing on the use of SCBs in terms of availability, motives for use and effects conducted in the US (Arfken et al. 2014; Meshack et al. 2013), New Zealand (Every-Palmer 2011), and with online communities of drug users (Kjellgren and Jonsson 2013; Spaderna et al. 2013; Soussan and Kjellgren 2014), whilst also adding to the previously understudied phenomena of development of dependence and withdrawal syndromes in users of the recently designed SCBs, 5f-AKB48 and 5F-PB-22. We recognise the limitations of this exploratory study given its smallscale and localised nature in a marginalised estate in the Republic. Of interest is the clustering of sole use of these SCBs amongst these users, and the rapid and harmful development of dependence for these individuals.

We were committed to ensuring that the user's experience was undistorted by any pre conceived research understanding in analysis (Levasseur 2003). Validity in the form of '*trustworthiness*' of the data (Lincoln and Guba 1985; Wallendorf and Belk 1989), was strengthened

by verification of extensive horizontal and vertical similarities across these realist descriptions of experiences and subsequent partial phenomenological psychological reduction (Karlsson 1995). Supporting prior literature (Fattore and Fratta 2011; Gunderson et al. 2012; Spaderna et al. 2013), reasons for initial experimentation centred on boredom, low awareness of risk and widespread availability of mixtures in this estate. Smoking was the only route of administration and in order to enhance the effect, rarely in combination with tobacco. Awareness of harm was low, and similar to other studies (EMCDDA 2009; Every-Palmer 2011; Fattore and Fratta 2011; Gunderson et al. 2012; Seely et al. 2012; Seely et al. 2011) underpinned by the initial belief that herbal smoking mixtures were safe and natural, and an acceptable potent alternative to natural cannabis. Acute differences between spectrum and intensity of synthetic and natural cannabis are present (Brents et al. 2011; 2012; Spaderna et al. 2013), with the short lived psycho-stimulant effect and development of compulsive regular use within short time frames differing to the longer lasting effects of natural cannabis. Some studies report that herbal SCB users prefer the effects of natural cannabis to the synthetic variety (Arfken et al. 2014; Winstock and Barratt 2013).

First-time experiences were intensely pleasurable characterised by euphoria, calmness, relaxation and feeling of well-being despite nausea, and with desire to repeat (Fattore and Fratta 2011; Kjellgren and Jonsson 2013; Schnier et al. 2011). Once all contents were smoked, happy and calm feelings receded and were replaced by feelings of agitation and restlessness. Whilst the reported effects are described in other studies (Fattore and Fratta 2011; Kjellgren and Jonsson 2013; Schnier et al. 2011), in contrast, solitary smoking of herbal mixtures was preferred within the private home setting. Subjective and physiologic (both dissociative and psycho-stimulant) effects and duration reportedly varied depending on content of the mixture (Schifano et al. 2006, 2009; Winstock and Barratt 2013) with some containing 5f-AKB48 and 5F-PB-22 in combination. Acute physical withdrawal symptoms are similar to those reported in the literature (see Helander et al. 2013; Seely et al. 2011; Simmons et al. 2011), and included internal restless, urge to re-dose, chest pains and

pressure, tachycardia and palpitations, lower extremity pain and spasms, nausea, sweating and emesis. Long term use was characterised by loss of appetite, cognitive impairment, breathlessness, cardiac conditions, skin ablations, tooth decay, lethargy, apathy, tremors and insomnia.

Most concerning in this study was the reporting of agitation, suicidal ideation and self-harm ideologies, and incidences of sibling and peer suicide during times of withdrawal and when attempted to restricted use or self-detoxify. Emergency hospital presentations have described presentations with severe agitation, panic attacks, tachycardia, nausea, paranoid ideation, and hallucinations post SCB use (Banerji et al. 2010; Bebarta et al. 2010; Sobolevsky et al. 2010; Vearrier and Osterhoudt 2010). SCB associated psychotic reactions (Castellanos et al. 2011; Every-Palmer 2010, 2011; Schneir et al. 2011; Spaderna et al. 2013), are often the common reason for the seeking of medical assistance (Forrester, et al.,2011) and can be prolonged and persistent, and sometimes never remit (Berry-Caban et al. 2013; Hurst et al. 2011; Tung et al. 2012; Van der Veer and Fiday 2011). Debates continue around whether use of herbal mixtures containing SCBs precipitates psychosis in individuals with and without history of psychotic disorders (Every-Palmer 2010; 2011; Hurst et al. 2011; Müller et al. 2010a,b; Pierre 2011).

Whilst research suggests the presence of three distinct groups of SCB users (marijuana users, casual users seeking to avoid detection, and naïve drug experimenters) (Seely et al. 2012), this study highlights the rapid addictive nature of herbal mixtures containing 5f-AKB48 and 5F-PB-22, where participants described quickly adopted dependent use patterns and routines. There appeared to be a blurring between comedown and withdrawal in user experiences over time. Development of dependence, tolerance over time, persistence of craving, continuous urge to consume despite adverse consequences, scarce attention to other interests or duties and clear withdrawal symptomatology in the event of protracted high dose use are well-documented in the case of SCBs (Fattore and Fratta 2011; Vardakou et al. 2010; Zimmermann et al. 2009). Dependent use in this study was characterised

by intense thought processes around seeking, using, re-dosing and sourcing, consumption at night in between sleeping, and the high SDS scores of participants.

However despite efforts to try to stop, unsuccessful attempts at ceasing use (one to four days abstinent) and self-detoxifying were reported and often with use of alcohol and cannabis to manage symptoms. Withdrawal reactions in other studies reportedly resolve within a week (Zimmermann et al. 2009; Rominger et al. 2013). Self-detoxification efforts in this study were further hampered by widespread social cues and contexts for use amongst networks of users and availability, alongside personal fears of psychosis and self-harm. Abstinence symptoms differed from natural cannabis in terms of the significant medical and psychiatric consequences (Budney and Stanger 2012), but with withdrawal syndromes acting as a negative reinforcers for use (Coffey et al. 2002; Gillespie et al. 2007; Chung et al. 2008). These symptoms resolved with resumed smoking of herbal mixtures. Of interest was that in contrast to SCB studies reporting poly substance use (Schifano et al. 2010; Vandrey et al. 2012; Winstock and Barratt 2013; Caviness et al. 2015), dependent users in this study smoked only the identified herbal mixtures containing 5f-AKB48 and 5F-PB-22, and used alcohol and cannabis only when attempting to self-detoxify in efforts to alleviate withdrawals. Severity of natural cannabis withdrawal has predictive validity in use of cannabis or other substances to alleviate symptoms (Copersino et al. 2006; Chung et al. 2008; Cornelius et al. 2008). The study highlights the need for the generation of evidence based medical and psychiatric treatment and detoxification protocols for this particularly severe form of synthetic cannabis withdrawal.

## **Conclusion**

The ever changing composition of herbal smoking mixtures and uneven consistency in the diverse range of new SCB's contributes to experiences of undesirable effects, psychiatric risks and the risks of accidental overdose (Uchiyama et al. 2010; Seely et al. 2012). This is, to our knowledge, the first study describing the development of dependence and withdrawal syndrome in dependent users of the



new SCB'S, 5f-AKB48 or 5F-PB-22, and contributes to the previously understudied phenomena of dependent use and withdrawal from SCB's. The study whilst small-scale and localised to a marginalised estate in Ireland highlights the rapid development of tolerance, regular dependent use within short timeframes and acute withdrawal symptomatology on cessation of use. Dependent use of mixtures containing SCBs is a concern given reporting of acute CNS and cardiovascular toxicity with severe cardiovascular, gastrointestinal and psychiatric sequelae (Gunderson et al. 2012; Brents and Prather 2014). The wide variability of structure and pharmacological effects of SCB's, contributes to the recognition that mixtures containing SCBs should not be considered as homogenous products. Given the high affinity for the CB1R and CB2R receptor sites of some SCB's, and the implications of this on toxicity or withdrawal severity, further research is required to identify which SCBs are particularly toxic and most likely to cause severe withdrawal subsequent to dependence. Findings on these SCBs 5f-AKB48 and 5F-PB-22 warrant consideration in terms of informing policy and public health responses in Ireland where widely available. Continued specific evidence based psychiatric and clinical responses to treat withdrawal syndromes should be situated within expedited inter-agency pathways for detoxification, addiction counselling, crisis intervention and family support for dependent users. Training of key community and health professionals, and the design and implementation of harm reduction activity is also warranted.

### **Acknowledgements**

This work was supported by the Health Service Executive, and Teach na nDaoine, Ireland. The opinions expressed in this article are of the researchers and are not necessarily those of the funders.

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**Table 1 Empirical Phenomenological Psychological (EPP) five step method (Karlsson 1995)**

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| <p><b>Step 2.</b></p> | <p>The text was subsequently divided into smaller meaning units (MU), without regard to syntax, and each time a new meaning, focus or topic was introduced</p>  |
| <p><b>Step 3.</b></p> | <p>All MUs were transformed from the participants wording and restated by the research team in order to present the significant and implicit meaning of the dependence and withdrawal phenomena in objectivised terms. In order to obtain interpretative validity considerable efforts were made by the research team to ensure respect of the participants' experience</p> |
| <p><b>Step 4.</b></p> | <p>The restated MUs were then categorised by repeated consultation with the raw data, scrutinizing that the category itself was maintained, the understanding of what the phenomenon is (noema) and how it is expressed (noesis) and by considering specific characteristics and similarities in the dependence and withdrawal phenomena.</p>                               |
| <p><b>Step 5.</b></p> | <p>The generated categories then formed part of an abstraction process in order to create more general and overarching themes through the patterns identified within related categories.</p>  |

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